REMARKS

After entry of the present amendments, claims 1-4, 6-9, 11, 13-15, and 17-35 will be pending. Claims 1-4, 6-9, 11, 13-15, and 17 have been amended to correct typographical errors and to even more particularly describe the recited inventions. Claims 5, 10, 12, and 16 have been cancelled. Claims 18-35 have been added. Support for the new claims can be found throughout the specification, for example, at pages 13-15 and 108-125. No new matter has been added.

Information Disclosure Statement

Per a Telephone Interview with Examiner Perreira on March 9, 2007, no further action is required by the Applicants regarding the IDS submitted on September 24, 2004.

Rejections under 35 U.S.C. § 112

Claim 9 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because it is allegedly unclear "how much constitutes a therapeutically effective amount or how much is necessary to provide an effective radioactive composition." The Applicants respectfully disagree and request withdrawal of the rejection. It would be clear, using the information known in the art, in combination with the Applicants' disclosure, what a "therapeutically effective amount" would be. Indeed, Examiner Hartley, who is also associated with the examination of the instant application, has allowed claims reciting "therapeutically effective amount" in several patents, including U.S. Patent Nos. 7,160,559 (claims 10 and 13); 7,118,762 (claims 1, 13, and 17); and 6,685,913 (claims 1-7). The term "therapeutically effective amount" is a term of art well understood by those skilled in the art and is by no means "unclear," as alleged. The Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection.

Claims 11-14 stand rejected under 35 U.S.C. § 112. In light of the present amendments, these rejections are considered moot.

Rejections under 35 U.S.C. § 102

Claims 1, 4-6, 9-15, and 17 stand rejected under 35 U.S.C § 102(b) as allegedly anticipated by Freyne et al. (U.S. Patent No. 5,541,324). Claims 1-17 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Mabire et al. (WO02/28837). In both rejections, the Examiner has asserted that, due to the "natural abundance of ^{3}H," the compounds

disclosed in Freyne and Mabire would "inherently contain at least one radioactive atom." The Applicants respectfully disagree and request that the rejections be withdrawn.

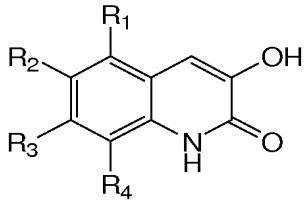
"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131. "To serve as an anticipation when the reference is silent about the asserted inherent characteristic[s], such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is *necessarily present* in the thing described in the reference." *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) (emphasis added); M.P.E.P § 2131.01(III). It is well established that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981).

The natural abundance of ^{3}H is one billionth of a billionth ($1x10^{-16}$) percent of natural hydrogen (see "Tritium," attached herewith); therefore, the Examiner has not established that any of the compounds disclosed in Freyne or Mabire ***necessarily*** contain at least one radioactive atom, as claimed in the present invention. None of the compounds described in Freyne or Mabire have been characterized as "radiolabelled" or "radioactive," as those terms are used in the present application. For at least these reasons, the Applicants request that the rejections be withdrawn.

Rejections under 35 U.S.C. § 103(a)

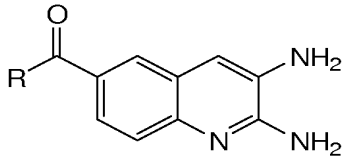
Claims 1-17 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Cai et al. (U.S. Patent No. 5,597,922) in view of Freyne et al. (U.S. Patent No. 5,541,325). The Applicants respectfully disagree.

The Examiner notes that Cai discloses compounds having the formula:



The Examiner further notes that Cai does not disclose the same phenyl substitutents R_{1-4} as those of the instant claims. The Examiner has applied Freyne as encompassing the phenyl

substituents of the present invention. Notably, however, Freyne discloses compounds of the following formula:



The compounds described by Cai and Freyne are structurally dissimilar, each possessing a different core structure, in addition to the variation in phenyl substituents. As such, one of skill in the art would *not* have been motivated to modify Cai in light of Freyne in order to produce compounds of the present invention. Moreover, Cai describes compounds that exhibit *glycine* receptor antagonist activity. Cai at col. 4, lines 9-10. Freyne describes compounds that exhibit inhibition activity against *phosphodiesterase* isoenzymes. Freyne at col. 20, lines 57-62. In contrast to both Cai and Freyne, the compounds of the present invention exhibit *glutamate* (mGluR) antagonist activity. Specification at page 32, lines 26-30. As a result, one of skill in the art would not have been motivated to modify the glycine antagonists of Cai with the phosphodiesterase inhibitors of Freyne at arrive at the glutamate antagonists of the present invention. For at least these reasons, a *prima facie* case of obviousness has not been made, and the Applicants respectfully request withdrawal of the rejection.

Claims 1-17 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Cai et al. in view of Mabire. The Applicants respectfully disagree.

Cai discloses that the compounds described therein "may be used" to characterize the *glycine* binding site, describing that preferred compounds for this purpose are isotopically labeled compounds. Cai at col. 57, lines 33-40. Mabire discloses compounds that bind to the *glutamate* receptor, but contains no teaching or suggestion regarding the radiolabeling of such compounds. The Office Action fails to explain why those skilled in the art would be motivated to combine these references. Absent the guidance of the instant application, one of skill in the art would not be motivated to modify the glutamate receptor antagonists of Mabire to produce the radiolabelled compounds of the present invention. The Applicants respectfully request withdrawal of the rejection.

Non-Statutory Obviousness-Type Double-Patenting Rejection

Claims 1-6, 9-15, and 17 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over pending claims 1-4, 8, 9, 11, 15, 18, and 19 of U.S. Application No. 11/133,678. The Applicants respectfully traverse. The instant invention is directed to radiolabeled compounds and methods of using such compounds. The pending claims of U.S. App. No. 11/133,678 are directed to non-radiolabeled compounds; therefore, the claims of U.S. App. No. 11/133,678 do not encompass the claims of the present invention. The Applicants request that the rejection be withdrawn.

The Applicants respectfully submit that the foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants submit that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 215-564-8918.

Date: April 4, 2007

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Tritium (Hydrogen-3)

Symbol:	**H** (H-3)
Atomic Number: *(protons in nucleus)*	**1**
Atomic Weight: *(naturally occurring H)*	**1**

What Is It? Tritium is the only radioactive isotope of hydrogen. (An isotope is a different form of an element that has the same number of protons in the nucleus but a different number of neutrons.) The nucleus of a tritium atom consists of a proton and two neutrons. This contrasts with the nucleus of an ordinary hydrogen atom (which consists solely of a proton) and a deuterium atom (which consists of one proton and one neutron). Ordinary hydrogen comprises over 99.9% of all naturally occurring hydrogen. Deuterium comprises about 0.02%, and tritium comprises about a billionth of a billionth (10^{-16} percent) of natural hydrogen.

Radioactive Properties of Tritium

Isotope	Half-Life *(yr)*	Natural Abundance *(%)*	Specific Activity *(Ci/g)*	Decay Mode	Radiation Energy *(MeV)*		
					Alpha *(α)*	Beta *(β)*	Gamma *(γ)*
H-3	12	<<1	9,800	β	-	0.0057	-

Ci = curie, g = gram, and MeV = million electron volts; a dash means the entry is not applicable. (See the companion fact sheet on Radioactive Properties, Internal Distribution, and Risk Coefficients for an explanation of terms and interpretation of radiation energies.) Values are given to two significant figures.

The most common forms of tritium are tritium gas (HT) and tritium oxide, also called "tritiated water." In tritiated water, a tritium atom replaces one of the hydrogen atoms so the chemical form is HTO rather than H_2O. The chemical properties of tritium are essentially the same as those of ordinary hydrogen. It decays with a half-life of 12 years by emitting a beta particle to produce helium-3. Tritium has a relatively high specific activity and is generated by both natural and artificial processes. It is of concern at Department of Energy (DOE) sites that operated tritium production facilities, such as Hanford.

Where Does It Come From? Tritium is naturally present as a very small percentage of ordinary hydrogen in water, both liquid and vapor. This tritium is produced as a result of the interaction of cosmic radiation with gases in the upper atmosphere, and the natural steady-state global inventory is about 7.3 kilograms (kg). (About five times this amount remains from past atmospheric nuclear weapons tests.) After being produced in the atmosphere, it is readily incorporated into water and falls to earth as rain, thus entering the natural hydrological cycle. Tritium is also produced as a fission product in nuclear weapons tests and in nuclear power reactors, with a yield of about 0.01%. That is, about one atom of tritium is produced per 10,000 fissions. Each year a large commercial nuclear power reactor produces about 20,000 curies (2 grams) of tritium, which is generally incorporated in the nuclear fuel and cladding.

Because little tritium is naturally present, it must be produced artificially for use on a practical scale. Tritium can be made in production nuclear reactors, i.e., reactors designed to optimize the generation of tritium and special nuclear materials such as plutonium-239. Tritium is produced by neutron absorption of a lithium-6 atom. The lithium-6 atom, with three protons and three neutrons, and the absorbed neutron combine to form a lithium-7 atom with three protons and four neutrons, which instantaneously splits to form an atom of tritium (one proton and two neutrons) and an atom of helium-4 (two protons and two neutrons). The United States has recovered an estimated 225 kg of tritium, of which 150 kg has decayed into helium-3, leaving a current inventory of approximately 75 kg. While tritium can also be produced in accelerators by bombarding helium-3 with neutrons, this approach has not been proven on a large scale.

How Is It Used? Tritium is used as a component in nuclear weapons to boost the yield of both fission and thermonuclear (or fusion) warheads. Tritium is also used as a tracer in biological and environmental

studies, and as an agent in luminous paints such as those used to make building exit signs, airport runway lights, and watch dials.

What's in the Environment? Tritium is present in water (liquid and vapor) as a result of natural processes in the atmosphere, as well as from fallout from past atmospheric nuclear weapons tests and the operation of nuclear reactors and fuel reprocessing plants. The form of most concern, tritium oxide (HTO), is generally indistinguishable from normal water and can move rapidly through the environment in the same manner as water. Tritium is naturally present in surface waters at about 10 to 30 picocuries per liter (pCi/L). The maximum contaminant level developed by the Environmental Protection Agency for tritium in drinking water supplies is 20,000 pCi/L or 0.02 microcuries per liter (a picocurie is a millionth of a microcurie). Higher concentrations can be present in water at facilities that produce and utilize tritium, including certain DOE sites.

What Happens to It in the Body? Tritium can be taken into the body by drinking water, eating food, or breathing air. It can also be taken in through the skin. Nearly all (up to 99%) inhaled tritium oxide can be taken into the body from the lungs, and circulating blood then distributes it to all tissues. Ingested tritium oxide is also almost completely absorbed, moving quickly from the gastrointestinal tract to the bloodstream. Within minutes it is found in varying concentrations in body fluids, organs, and other tissues. Skin absorption of airborne tritium oxide can also be a significant route of uptake, especially for exposure to high concentrations of tritiated water vapor, as could occur under conditions of high humidity during hot weather, because of the normal movement of water through the skin. For someone immersed in a cloud of airborne tritium oxide (HTO), the uptake by absorption through the skin would be about half that associated with inhalation. No matter how it is taken into the body, tritium is uniformly distributed through all biological fluids within one to two hours. Tritium is eliminated from the body with a biological half-life of 10 days, the same as for water. During the time it is in the body, a small fraction of the tritium is incorporated into easily exchanged hydrogen sites in organic molecules.

What Is the Primary Health Effect? Tritium poses a health hazard only if it is taken into the body, because tritium decays by emitting a low-energy beta particle with no gamma radiation. This beta particle cannot penetrate deeply into tissue or travel far in air. The most likely form of uptake is as tritium oxide (or tritiated water), as the uptake of tritium gas is typically very low (less than 1%). Tritiated water behaves the same as ordinary water, both in the environment and in the human body. Hence, a significant fraction of the inhaled and ingested tritium is directly absorbed into the bloodstream. The health hazard of tritium is associated with cell damage caused by the ionizing radiation that results from radioactive decay, with the potential for subsequent cancer induction.

What Is the Risk? Lifetime cancer mortality risk coefficients have been calculated for nearly all radionuclides, including tritium *(see box at right)*. The values given here are for tritiated water; additional values are available, including for inhalation and ingestion of organically bound tritium and inhalation of tritium on particulates. As for other nuclides, the risk coefficient for tap water is about 80% of that for dietary ingestion.

Radiological Risk Coefficients

This table provides selected risk coefficients for inhalation and dietary ingestion of tritiated water. Risks are for lifetime cancer mortality per unit intake (pCi), averaged over all ages and both genders (10^{-12} is a trillionth). Other values, including for morbidity, are also available.

Isotope	Lifetime Cancer Mortality Risk	
	Inhalation (pCi^{-1})	Ingestion (pCi^{-1})
Tritium (H-3)	3.9×10^{-14}	4.4×10^{-14}

For more information, see the companion fact sheet on Radioactive Properties, Internal Distribution, and Risk Coefficients and the accompanying Table 1.